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# Effect of Vitamin D<sub>3</sub> Supplementation on Upper Respiratory Tract Infections in Healthy Adults

## The VIDARIS Randomized Controlled Trial

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THE ROLE OF VITAMIN D IN INFECTIOUS diseases and the potential impact of vitamin D supplementation as a preventive measure for infectious diseases are unclear.<sup>1</sup> Vitamin D has a role in both innate and adaptive immune responses. Of particular interest is the induction by vitamin D of cathelicidins, a group of antimicrobial peptides produced by neutrophils, macrophages, and epithelial cells. Epidemiological studies show an association between low vitamin D levels and a variety of respiratory tract infections. For example, vitamin D insufficiency is associated with increased risk of developing tuberculosis.<sup>1</sup>

The association of vitamin D insufficiency and susceptibility to viral respiratory tract infections is also un-

**Context** Observational studies have reported an inverse association between serum 25-hydroxyvitamin D (25-OHD) levels and incidence of upper respiratory tract infections (URTIs). However, results of clinical trials of vitamin D supplementation have been inconclusive.

**Objective** To determine the effect of vitamin D supplementation on incidence and severity of URTIs in healthy adults.

**Design, Setting, and Participants** Randomized, double-blind, placebo-controlled trial conducted among 322 healthy adults between February 2010 and November 2011 in Christchurch, New Zealand.

**Intervention** Participants were randomly assigned to receive an initial dose of 200 000 IU oral vitamin D<sub>3</sub>, then 200 000 IU 1 month later, then 100 000 IU monthly (n=161), or placebo administered in an identical dosing regimen (n=161), for a total of 18 months.

**Main Outcome Measures** The primary end point was number of URTI episodes. Secondary end points were duration of URTI episodes, severity of URTI episodes, and number of days of missed work due to URTI episodes.

**Results** The mean baseline 25-OHD level of participants was 29 (SD, 9) ng/mL. Vitamin D supplementation resulted in an increase in serum 25-OHD levels that was maintained at greater than 48 ng/mL throughout the study. There were 593 URTI episodes in the vitamin D group and 611 in the placebo group, with no statistically significant differences in the number of URTIs per participant (mean, 3.7 per person in the vitamin D group and 3.8 per person in the placebo group; risk ratio, 0.97; 95% CI, 0.85-1.11), number of days of missed work as a result of URTIs (mean, 0.76 days in each group; risk ratio, 1.03; 95% CI, 0.81-1.30), duration of symptoms per episode (mean, 12 days in each group; risk ratio, 0.96; 95% CI, 0.73-1.25), or severity of URTI episodes. These findings remained unchanged when the analysis was repeated by season and by baseline 25-OHD levels.

**Conclusion** In this trial, monthly administration of 100 000 IU of vitamin D did not reduce the incidence or severity of URTIs in healthy adults.

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clear. Several observational studies report an inverse association between serum 25-hydroxyvitamin D (25-OHD) levels and incidence of upper respiratory tract infections (URTIs).<sup>2-4</sup> Observational studies are potentially limited by reverse causality and residual confounding, and randomized controlled trials are necessary to properly assess whether there is an effect of vitamin D on risk of infection.<sup>5</sup> To date, however, the few clinical trials of vitamin D supplementation in adults to prevent URTIs have had conflicting results<sup>6-8</sup> and were limited in their ability to test the effect of vitamin D supplementation on URTI occurrence. For example, some were of short duration, used a relatively low dose of vitamin D, or were not designed to address URTI outcomes.

The current trial was established to determine the effect of vitamin D supplementation on incidence and severity of URTIs in healthy adults.

## METHODS

### Study Design and Participants

The study was a randomized, double-blind, placebo-controlled trial in Christchurch, New Zealand (latitude 43°S). Participants were staff or students of the Canterbury District Health Board, the regional publicly funded health care organization, or the University of Otago, Christchurch, who were aged 18 years or older, were able to give written informed consent, and who anticipated that they would be a resident of the Christchurch region for the study period. Following an advertising campaign, we screened and enrolled volunteers during February through April 2010.

Exclusion criteria were (1) use of vitamin D supplements other than as part of a daily multivitamin preparation (in which the daily intake was  $\leq 400$  IU); (2) use of immunosuppressants or medications that interfere with vitamin D metabolism (eg, thiazide diuretics, phenytoin, carbamazepine, primidone, phenobarbital, doses of prednisone  $>10$  mg/d, methotrexate, azathioprine, cyclosporin); (3) his-

tory of hypercalcemia or nephrolithiasis; (4) sarcoidosis; (5) kidney disorders requiring dialysis or polycystic kidney disease; (6) cirrhosis; (7) current malignancy diagnosis in which the cancer was aggressive and prognosis was poor; (8) baseline plasma calcium (corrected for plasma albumin concentration) greater than 10.4 mg/dL or less than 8.4 mg/dL; (9) enrollment or planned enrollment in other research that would conflict with full participation in the study or confound the observation or interpretation of the study findings (eg, in which 25-OHD levels were tested and results known by the participant; in which the participant was required to take conflicting medications; any investigations of viruses and antiviral treatments); and (10) pregnancy or planned pregnancy during the study period.

The study was approved by the Upper South B Regional Ethics Committee and all participants provided written informed consent.

### Randomization and Masking

Participants were assigned using computer-generated randomization to receive either vitamin D<sub>3</sub> or placebo. Participants randomized to the active treatment received oral vitamin D<sub>3</sub>, 200 000 IU, then 200 000 IU 1 month later, then 100 000 IU monthly thereafter for a total of 18 months. This dosing regimen was chosen with the aim of achieving mean 25-OHD levels of about 40 ng/mL,<sup>9,10</sup> which, at the time of the study, was in the 25-OHD range with the lowest risk of disease in observational studies. (To convert 25-OHD to nmol/L, multiply by 2.496.) Monthly dosing also helped ensure adherence to treatment. Those randomized to placebo received matching inactive tablets administered in a dosing regimen identical to the active treatment.

Both vitamin D<sub>3</sub> and placebo tablets were sourced from Tishcon Corp and were identical in appearance. The randomization process and bottling of tablets were performed in Auckland, New Zealand, under the supervision of the

study biostatistician (A.W.S.) to ensure that those running the study, including outcome assessors and those administering the intervention, were blinded to allocation. Research staff directly administered all treatments to participants during monthly visits throughout the study period.

### Procedures

Information on baseline characteristics was obtained by interviewer-administered questionnaire at the screening visit and included data on demographics, occupation, medical history, smoking, current medications, and supplement use.

After randomization, follow-up visits occurred monthly until the end of the study. During these visits, dedicated study staff met the participants in person, administered their monthly dose of vitamin D or placebo, and administered a brief questionnaire. This questionnaire asked about episodes of respiratory tract illness during the preceding month that had not already been reported to study personnel and also noted any changes in medications or supplement use and adverse events.

In addition to the monthly visits, participants were asked to contact study staff whenever they experienced a URTI, defined as the sudden onset of 1 or more of runny nose, nasal stuffiness, sore throat, or cough that the participant did not attribute to allergy. A research staff member then visited the participant to complete a symptom survey (Wisconsin Upper Respiratory Symptom Survey 24 [WURSS-24])<sup>11</sup> and collect a nasopharyngeal swab sample. The WURSS-24 is an instrument for assessing the severity and functional impact of URTIs; it contains 24 items, each based on 7-point Likert-type severity scales, and comprises the same items as an earlier version (WURSS-21<sup>12-15</sup>) plus items for headache, body ache, and fever. The WURSS-24 was completed daily over subsequent days through telephone interview by research staff or by self-reported questionnaire until the individual had reported 2 consecutive days



of “not sick,” or until 14 days after the onset of the URTI. For those whose URTI symptoms ended before 14 days, the duration of the episode was recorded as ending the day before 2 consecutive “not sick” days. The number of days of missed work as a result of the URTI was also recorded.

Nasopharyngeal swab samples were tested for the following respiratory viruses by real-time polymerase chain reaction (Fast Track Diagnostics): adenovirus; bocavirus; coronaviruses 229E, OC43, NL63, and HKU; enterovirus; influenza A and B viruses; human metapneumoviruses A and B; human rhinovirus; parainfluenza viruses 1 to 4; parechovirus; and respiratory syncytial viruses A and B.

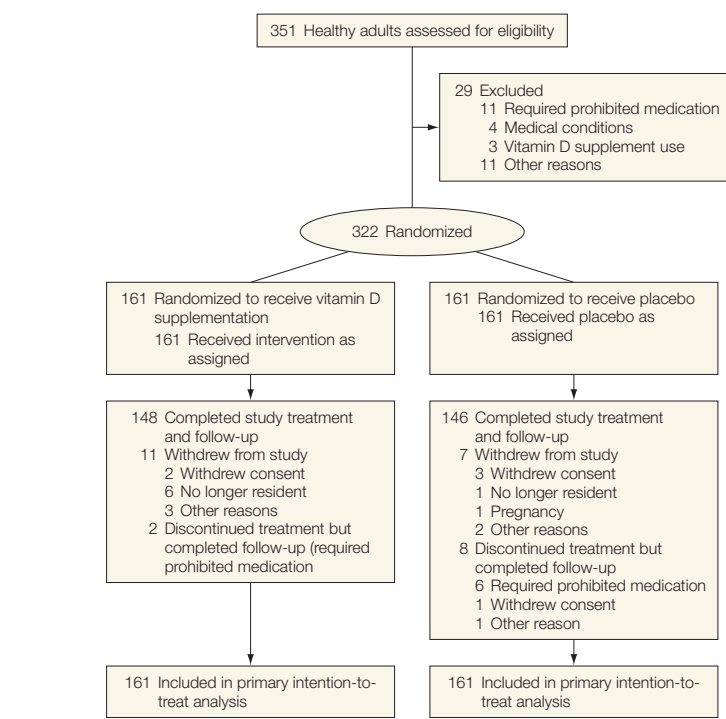
The primary end point was number of URTI episodes. Secondary end points were number of days of missed work as a result of URTI episodes, duration of URTI episodes, severity of URTI episodes, and detection of respiratory viruses in nasopharyngeal samples.

Plasma calcium and serum 25-OHD levels were measured at baseline and at 2, 6, 12, and 18 months after enrollment. Plasma calcium was measured in real time to monitor safety (Abbott c8000 analyzer, Abbott Laboratories). Serum samples for 25-OHD measurement were stored at  $-112^{\circ}\text{F}$  ( $-80^{\circ}\text{C}$ ) until each participant completed the study. All samples from each participant were batched and analyzed within the same run. The 25-OHD levels were measured by liquid chromatography–tandem mass spectrometry (ABSciex API 4000) and the results were unknown to the study team until after completion of the study.

### Statistical Analysis

On the assumption that participants would have an average of 1.6 URTIs per year<sup>16,17</sup> and follow-up of 18 months and that the intervention would need to reduce the mean number of infections by 20% to have clinical relevance, we calculated that a sample of 240 participants would be required to observe this effect with a power of 80% at the .05 level of significance. This number was

**Figure 1.** Participant Flow



increased to 320 to compensate for the potential influence of influenza vaccination and loss to follow-up.

The numbers of URTI events for each participant were summed and then compared between the treatment and placebo groups using a negative binomial model that included a dispersion parameter. This model was then extended to include variables that might indicate participant subgroups with different patterns of effect. These binary variables included winter season (May–September), positive nasopharyngeal swab, and season-adjusted baseline serum 25-OHD value less than 20 ng/mL (50 nmol/L). Analysis of the number of days of missed work also used a negative binomial model but because there were multiple events for many participants, a generalized estimating equation model with an exchangeable correlation matrix was used.

A comparison of the sum of the WURSS-24 scores in the first 7 days of the URTI event was made using a general linear mixed model and modeling

the participants as random effects. For participants who had incomplete data on the WURSS-24, missing observations were estimated using multiple imputation (5 imputations) using the Markov chain Monte Carlo method on natural log scores (with a constant of 1 added).<sup>18</sup>

Duration of URTI events was assessed using the Cox proportional hazard model with multiple events per participant being treated as clustered events and using robust sandwich covariance matrix estimates.

The  $\alpha$  level/hypothesis testing was 2-sided with statistical significance set at  $P < .05$ . The statistical software used was SAS, version 9.2 (SAS Institute Inc).

## RESULTS

### Study Recruitment and Follow-up

FIGURE 1 shows the study flow diagram. Of 351 potential participants screened, 322 were eligible for inclusion and were randomly assigned to a treatment group. Two hundred ninety-four participants (91%) completed the study treatment and follow-up, 18 (6%)



**Table 1.** Baseline Characteristics

Characteristics	Participants, No. (%) <sup>a</sup>	
	Vitamin D (n = 161)	Placebo (n = 161)
Age, mean (SD), y	47 (10)	48 (10)
Female	121 (75)	120 (75)
Ethnicity <sup>b</sup>		
European	154 (96)	149 (93)
Maori	7 (4)	7 (4)
Asian	3 (2)	5 (3)
Pacific peoples	0	1 (1)
Other	2 (1)	3 (2)
Work		
High patient contact	58 (36)	48 (30)
Some patient contact	46 (29)	45 (28)
No patient contact	57 (35)	68 (42)
Height, mean (SD), cm	168 (9)	168 (9)
Weight, mean (SD), kg	77 (15)	78 (15)
Body mass index, mean (SD) <sup>c</sup>	27 (5)	28 (5)
Smoking status		
Current	6 (4)	11 (7)
Ex-smoker	36 (22)	42 (26)
Never	119 (74)	108 (67)
Influenza vaccination <sup>d</sup>		
None	76 (47)	87 (54)
Seasonal influenza	47 (29)	39 (24)
Influenza A(H1N1)	20 (12)	14 (9)
Seasonal and influenza A(H1N1)	18 (11)	21 (13)
Asthma	37 (23)	34 (21)
Chronic bronchitis or emphysema	6 (4)	2 (1)
Diabetes	3 (2)	1 (1)
Serum 25-hydroxyvitamin D level, mean (SD), ng/mL	29 (9)	28 (9)
Plasma calcium level, mean (SD), mg/dL <sup>e</sup>	9.2 (0.4)	9.2 (0.4)

<sup>a</sup>Data are expressed as No. (%) of participants unless otherwise indicated.

<sup>b</sup>Ethnic groups are those used for the New Zealand Census. European: New Zealand European, English, Dutch, British, Australian, European; Asian: Chinese, Indian, Korean, Filipino, Japanese, Sri Lankan, Cambodian, Thai; Pacific peoples: Samoan, Cook Islands Maori, Tongan, Niuean, Fijian, Tokelauan, Tuvaluan; other: Middle Eastern, Latin American, African. Participants could identify with more than 1 ethnic group; therefore, percentages do not add to 100.

<sup>c</sup>Calculated as weight in kilograms divided by height in meters squared.

<sup>d</sup>Vaccination question asked at 1 month of study and included all vaccinations prior to and post baseline. Two vaccinations for influenza were available: influenza A(H1N1) alone and seasonal influenza, which contained 3 influenza strains including influenza A(H1N1).

<sup>e</sup>Plasma calcium values stated are corrected for plasma albumin concentration.

322 participants were included in the intention-to-treat analysis. There were only 3 missed appointments throughout the study.

### Baseline Characteristics

TABLE 1 shows the baseline characteristics of the participants. Overall, the mean age at recruitment was 47 years and 241 (75%) were female. The groups were evenly balanced on all characteristics.

### URTI Episodes

Characteristics of the URTI episodes are shown in TABLE 2. There were a total of 1204 URTI episodes reported throughout the study period (mean, 3.7 [range, 0-17] and median, 3 [interquartile range [IQR], 2-5] episodes per person), including 593 URTI episodes in the vitamin D group (mean, 3.7 [range, 0-17] and median, 3 [IQR, 2-5]) and 611 episodes in the placebo group (mean, 3.8 [range, 0-12] and median, 4 [IQR, 2-5]). Of the 1204 URTI episodes, 762 were spontaneously reported to study staff and 442 episodes were reported during regular monthly follow-up visits. Only 7 participants in the vitamin D group and 6 participants in the placebo group reported no URTI episodes throughout the entire study period. There were no statistically significant differences in the duration or severity of URTI episodes, in the number of days of missed work as a result of URTI episodes, or in the number of URTI episodes associated with positive nasopharyngeal swabs (Table 2).

The severity findings were unchanged when the data analyzed using WURSS-24 scores were summed over 14 days rather than 7 days, or when the WURSS-21 was used to measure severity (Table 2). The 442 URTI episodes that were not spontaneously reported were evenly distributed between the vitamin D and placebo groups (213 and 229, respectively). Fewer than half of URTI episodes resulted in any missed work (154 [41%] of 380 spontaneously reported episodes in the vitamin D group and 157 [41%] of 382 spon-

taneously reported episodes in the placebo group).

Overall, respiratory viruses were detected in 342 (50%) of 686 URTI episodes for which nasopharyngeal swabs were collected; the main reason for non-collection of swabs was that the participant was out of town when the URTI was reported. The most common viruses detected were human rhinoviruses and coronaviruses (Table 2). Influenza viruses were detected in only 4 episodes.

There was no interaction of treatment effect and URTIs between winter and summer ( $P = .52$ ); mean number of URTI episodes during summer months was 1.3 for both treatment groups and during winter was 2.5 and 2.3 for the placebo and vitamin D groups, respectively. Both influenza seasons during the study period were relatively mild.

### Serum 25-OHD Levels

The mean baseline 25-OHD level was 29 (SD, 9) ng/mL, and only 5 participants (1.6%) had levels less than 10 ng/mL. FIGURE 2 shows mean 25-OHD levels among the intention-to-treat population. Vitamin D supplementation resulted in a steep increase in 25-OHD levels that was maintained throughout the study period. No statistically significant differences were noted for any outcome when the data were reanalyzed by baseline 25-OHD levels less than 20 ng/mL. Only 13 participants (all in the placebo group) had 25-OHD levels consistently less than 20 ng/mL throughout the study duration.

### Safety

Mean corrected plasma calcium levels did not differ between the vitamin D and placebo groups at any time during the study period (mean, 9.2 [SD, 0.4] mg/dL for both treatment groups and at all time points). There were no cases of asymptomatic hypercalcemia (corrected plasma calcium >10.4 mg/dL). There were 40 serious adverse events (21 in the vitamin D group and 19 in the placebo group) and 1492 other

withdrew from the study altogether, and 10 (3%) withdrew from treatment but completed the 18-month follow-up. All



**Table 2.** Outcome Measures by Study Group

Outcome Measures	Vitamin D (n = 161)	Placebo (n = 161)	Vitamin D vs Placebo	
			Risk Ratio (95% CI)	P Value
No. of URTI episodes	593	611		
No. of URTIs per person				
Mean (SD)	3.7 (2.4)	3.8 (2.2)	0.97 (0.85-1.11)	.65
Median (IQR)	3 (2-5)	4 (2-5)		
No. of days of missed work per episode <sup>a</sup>				
Mean (SD)	0.76 (1.25)	0.76 (1.26)	1.03 (0.81-1.30)	.82
Median (IQR)	0 (0-1)	0 (0-1)		
Duration of symptoms per episode, median (25th percentile), d <sup>a,b</sup>	12 (8)	12 (7)	0.96 (0.73-1.25)	.76
URTI severity per episode, median (IQR) <sup>a,c</sup>	171 (86-295)	183 (97-316)		.48
No. (%) of URTI episodes with positive respiratory virus swab <sup>a,d</sup>	177 (51)	166 (49)		
Rhinoviruses	83 (24)	70 (21)		
Coronaviruses	74 (21)	60 (18)		
Parainfluenza viruses	12 (3)	18 (5)		
Human metapneumovirus	3 (0.9)	9 (3)		
Respiratory syncytial virus	2 (0.6)	7 (2)		
Influenza A	2 (0.6)	2 (0.6)		
Other viruses	23 (7)	25 (7)		
No viruses	170 (49)	174 (51)		

Abbreviations: IQR, interquartile range; URTI, upper respiratory tract infection.

<sup>a</sup>Analyzed for spontaneously reported URTI episodes (vitamin D, n=380; placebo, n=382).

<sup>b</sup>Vitamin D, n=366; placebo, n=365.

<sup>c</sup>Sum of Wisconsin Upper Respiratory Symptom Survey (WURSS) 24 scores during the first 7 days of the URTI (vitamin D, n=351; placebo, n=351). The corresponding scores for the WURSS-21 were 162 (84-276) vs 167 (91-290), respectively.

<sup>d</sup>No swab information available for 34 URTI events in the vitamin D group and 42 URTI events in the placebo group. Multiple viruses were detected in some swabs.

adverse events (700 in the vitamin D group and 792 in the placebo group) recorded during the study, none of which was thought to be related to vitamin D supplementation (TABLE 3).

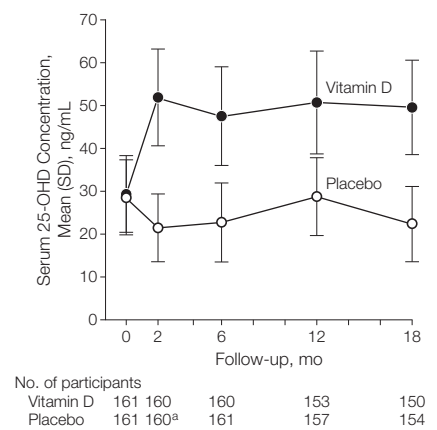
## COMMENT

The main finding from this study is that a monthly dose of 100 000 IU of vitamin D<sub>3</sub> in healthy adults did not significantly reduce the incidence or severity of URTIs. This result remained unchanged when the analysis included winter season or baseline 25-OHD levels.

This finding is consistent with 2 other randomized controlled trials that were specifically designed to assess whether vitamin D supplementation prevents acute respiratory infections in adults. Li-*Ng et al*<sup>8</sup> found no decrease in the incidence or severity of URTIs with vitamin D supplementation during winter in 162 adults. However, this study was of short duration (12 weeks), was underpowered, and first administered vitamin D<sub>3</sub> during (rather than before) winter. Laaksi *et al*<sup>7</sup> also found no

difference in their primary outcome (number of days absent from duty owing to respiratory tract infection) in 164 soldiers randomized to vitamin D<sub>3</sub> (400 IU/d) or placebo for 6 months during winter, although the overall proportion of participants who had no days absent from duty was higher in the vitamin D group. This study was also underpowered and the relatively low dose of vitamin D<sub>3</sub> resulted in only 29% of those in the intervention group obtaining 25-OHD levels greater than 32 ng/mL. In an adjunct to a trial investigating vitamin D supplementation as an intervention to prevent fractures in elderly people, there was no statistically significant relationship between treatment group and having had an infection or taking antibiotics during a week in winter.<sup>6</sup>

Two recent studies showed differing effects of vitamin D supplementation in children. A randomized trial of daily vitamin D supplementation in Mongolian schoolchildren in winter, a population with an average 25-OHD level of less than 10 ng/mL, found a 50%

**Figure 2.** Mean Serum 25-Hydroxyvitamin D (25-OHD) Levels Among the Intention-to-Treat Population

Error bars indicate standard deviation. Error bars incorporate both between-participant error and variation due to the taking of blood over a 3-month period at each follow-up point.

<sup>a</sup>One specimen was missing from this time point; therefore, the mean 25-OHD level is derived from 159 specimens.

reduction in acute respiratory infections.<sup>19</sup> In contrast, vitamin D supplementation did not affect the incidence



**Table 3.** Summary of Serious Adverse Events by Study Group

Serious Adverse Events	Vitamin D (n = 21)	Placebo (n = 19)
Cancer diagnosis/treatment <sup>a</sup>	4	1
Surgical procedure		
Acute <sup>b</sup>	3	5
Elective <sup>c</sup>	8	5
Trauma <sup>d</sup>	3	6
Treatment for medical condition <sup>e</sup>	3	2

<sup>a</sup>Four participants had breast cancer (vitamin D, n=3; placebo, n=1); of these, 1 in the vitamin D group withdrew from the study following diagnosis. One participant had an abdominal desmoid tumor.

<sup>b</sup>Surgery included 2 appendectomies (vitamin D, n=1; placebo, n=1); 1 cholecystectomy (vitamin D); drainage of a spontaneous pneumothorax (vitamin D); and 4 separate instances in which 1 participant had a breast abscess drained and excised (placebo).

<sup>c</sup>Surgery included 3 hysterectomies (vitamin D, n=1; placebo, n=2); 1 repair of a prolapsed bladder (vitamin D); 1 repair of a vaginal prolapse (vitamin D); 2 hip replacements (vitamin D); 1 spinal fixation and stabilization (vitamin D); 1 rotator cuff repair (vitamin D); 1 knee replacement (vitamin D); 1 embolization of uterine fibroid (placebo); 1 nasal surgery for sleep apnea (placebo); and 1 septoplasty and removal of turbinates (placebo).

<sup>d</sup>Injuries related to 4 bicycle accidents (vitamin D, n=2; placebo, n=2) and 5 falls (vitamin D, n=1; placebo, n=3).

<sup>e</sup>One pneumonia (vitamin D); 1 gastroenteritis (placebo); 1 diabetes complication (placebo); 1 cellulitis (vitamin D); and 1 supraventricular tachycardia (vitamin D).

of first episodes of pneumonia in 1524 infants from Afghanistan, another population with a high prevalence of vitamin D deficiency.<sup>20</sup>

Strengths of our study include the relatively large sample size, the 18-month duration, and the high dose of vitamin D<sub>3</sub> administered (with a loading dose), thus avoiding the shortcomings of previous adult studies. Our dosing regimen, started during summer/fall, resulted in sustained mean 25-OHD levels greater than 48 ng/mL throughout the study period in those in the intervention group. Other strengths are the rigorous efforts to capture URTI episodes and the collection of virological data.

We did not show a benefit of vitamin D supplementation in our study population; however, it is possible that vitamin D may prevent URTIs in other populations. The mean baseline 25-OHD level was 29 ng/mL, and the mean level decreased to about 20 ng/mL during the winter in the placebo group; only 5 participants (1.6%) had baseline levels less than 10 ng/mL. It is possible that an effect may be observed in

a population with a higher prevalence of vitamin D deficiency, as occurred in a recent trial of vitamin D supplementation to reduce exacerbations of chronic obstructive pulmonary disease.<sup>21</sup> In that trial, vitamin D supplementation significantly reduced exacerbations only in patients with baseline 25-OHD levels less than 10 ng/mL.

We were also unable to assess the effect of vitamin D supplementation on prevention of infection caused by individual viruses. Of particular note, there were few cases of confirmed influenza infection among our partly vaccinated group of participants. Although adult data are unavailable, a randomized controlled trial in Japanese schoolchildren, set up to assess the effect of vitamin D supplementation on “doctor-diagnosed influenza,” did not report on that outcome but did report a statistically significant reduction in laboratory-confirmed influenza A infection (relative risk, 0.58; *P*=.04).<sup>22</sup>

Would the results of our study have been different if we had given participants vitamin D, 3300 IU/d, as opposed to 100 000 IU monthly? Opposite outcomes have been documented for trials of 4-monthly vs annual dosing regimens of vitamin D supplementation for risk of fractures.<sup>23,24</sup> Several mechanisms have been proposed to explain how various dosing regimens may have different effects on immune function.<sup>25</sup> However, it is purely speculative at this stage as to whether some conditions (eg, infections) require a smaller steady dose of vitamin D supplementation for benefit. Alternatively, genetic variation in vitamin D metabolism or signaling may modify the anti-infective effects of vitamin D. Vitamin D receptor polymorphisms have been linked to both susceptibility to tuberculosis<sup>26</sup> and response to vitamin D supplements in patients with tuberculosis.<sup>27</sup>

With regard to safety, our regimen of monthly 100 000-IU doses of vitamin D<sub>3</sub> was more than 5 times the recommended daily allowance of 600 IU for adequacy in adults,<sup>28</sup> yet we documented no episodes of hypercalcemia

and no adverse events attributed to vitamin D. Another recent study of 182 adults with moderate to severe chronic obstructive pulmonary disease reported 4 cases of mild asymptomatic hypercalcemia in those receiving monthly 100 000-IU doses of vitamin D without a loading dose.<sup>21</sup> All 4 cases were noted 4 months after starting treatment and spontaneously resolved with normal calcium levels at 8 and 12 months, despite continuation of study medication.

In conclusion, we report that monthly administration of 100 000-IU doses of vitamin D<sub>3</sub> did not reduce the incidence or severity of URTIs in healthy, predominantly European adults with near-normal vitamin D levels. Further research is required to clarify whether there is benefit from supplementation in other populations and with other dosing regimens.

**Author Contributions:** Dr Murdoch had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Study concept and design:** Murdoch, Chambers, Jennings, Stewart, Priest, Florkowski, Livesey, Camargo, Scragg.

**Acquisition of data:** Murdoch, Slow, Chambers, Jennings, Florkowski, Livesey.

**Analysis and interpretation of data:** Murdoch, Slow, Chambers, Jennings, Stewart, Priest, Florkowski, Livesey, Camargo, Scragg.

**Drafting of the manuscript:** Murdoch.

**Critical revision of the manuscript for important intellectual content:** Murdoch, Slow, Chambers, Jennings, Stewart, Priest, Florkowski, Livesey, Camargo, Scragg.

**Statistical analysis:** Murdoch, Stewart, Florkowski.

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**Study supervision:** Murdoch, Chambers.

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## REFERENCES

1. Khoo AL, Chai L, Koenen H, Joosten I, Netea M, van der Ven A. Translating the role of vitamin D<sub>3</sub> in infectious diseases. *Crit Rev Microbiol*. 2012;38(2):122-135.
2. Ginde AA, Mansbach JM, Camargo CA Jr. Association between serum 25-hydroxyvitamin D level and upper respiratory tract infection in the Third National Health and Nutrition Examination Survey. *Arch Intern Med*. 2009;169(4):384-390.
3. Karatekin G, Kaya A, Salihoğlu Ö, Balci H, Nuhoglu A. Association of subclinical vitamin D deficiency in newborns with acute lower respiratory infection and their mothers. *Eur J Clin Nutr*. 2009;63(4):473-477.
4. Laaksi I, Ruohola J-P, Tuohimaa P, et al. An association of serum vitamin D concentrations <40 nmol/L with acute respiratory tract infection in young Finnish men. *Am J Clin Nutr*. 2007;86(3):714-717.
5. Sattar N, Welsh P, Panarelli M, Forouhi NG. Increasing requests for vitamin D measurement: costly, confusing, and without credibility. *Lancet*. 2012;379(9811):95-96.
6. Avenell A, Cook JA, MacLennan GS, Macpherson GC. Vitamin D supplementation to prevent infections: a sub-study of a randomised placebo-controlled trial in older people (RECORD trial, ISRCTN 51647438). *Age Ageing*. 2007;36(5):574-577.
7. Laaksi I, Ruohola J-P, Mattila V, Auvinen A, Ylikomi T, Pihlajamäki H. Vitamin D supplementation for the prevention of acute respiratory tract infection: a randomized, double-blinded trial among young Finnish men. *J Infect Dis*. 2010;202(5):809-814.
8. Li-Ng M, Aloia JF, Pollack S, et al. A randomized controlled trial of vitamin D<sub>3</sub> supplementation for the prevention of symptomatic upper respiratory tract infections. *Epidemiol Infect*. 2009;137(10):1396-1404.
9. Ilahi M, Armas LAG, Heaney RP. Pharmacokinetics of a single, large dose of cholecalciferol. *Am J Clin Nutr*. 2008;87(3):688-691.
10. Vieth R, Chan P-CR, MacFarlane GD. Efficacy and safety of vitamin D<sub>3</sub> intake exceeding the lowest observed adverse effect level. *Am J Clin Nutr*. 2001;73(2):288-294.
11. Barrett B, Hayney MS, Muller D, et al. Meditation or exercise for preventing acute respiratory infection: a randomized controlled trial. *Ann Fam Med*. 2012;10(4):337-346.
12. Barrett B, Brown R, Mundt M. Comparison of anchor-based and distributional approaches in estimating important difference in common cold. *Qual Life Res*. 2008;17(1):75-85.
13. Barrett B, Brown R, Mundt M, et al. The Wisconsin Upper Respiratory Symptom Survey is responsive, reliable, and valid. *J Clin Epidemiol*. 2005;58(6):609-617.
14. Barrett B, Locken K, Maberry R, et al. The Wisconsin Upper Respiratory Symptom Survey (WURSS): a new research instrument for assessing the common cold. *J Fam Pract*. 2002;51(3):265.
15. Barrett B, Brown RL, Mundt MP, et al. Validation of a short form Wisconsin Upper Respiratory Symptom Survey (WURSS-21). *Health Qual Life Outcomes*. 2009;7:76.
16. Jennings LC, MacDiarmid RD, Miles JAR. A study of acute respiratory disease in the community of Port Chalmers, I: illnesses within a group of selected families and the relative incidence of respiratory pathogens in the whole community. *J Hyg (Lond)*. 1978;81(1):49-66.
17. Monto AS, Sullivan KM. Acute respiratory illness in the community: frequency of illness and the agents involved. *Epidemiol Infect*. 1993;110(1):145-160.
18. Schafer JL. *Analysis of Incomplete Multivariate Data*. New York, NY: Chapman & Hall; 1997.
19. Camargo CA Jr, Ganmaa D, Frazier AL, et al. Randomized trial of vitamin D supplementation and risk of acute respiratory infection in Mongolia. *Pediatrics*. 2012;130(3):e561-e567.
20. Manaseki-Holland S, Maroof Z, Bruce J, et al. Effect on the incidence of pneumonia of vitamin D supplementation by quarterly bolus dose to infants in Kabul: a randomised controlled superiority trial. *Lancet*. 2012;379(9824):1419-1427.
21. Lehouck A, Mathieu C, Carremans C, et al. High doses of vitamin D to reduce exacerbations in chronic obstructive pulmonary disease: a randomized trial. *Ann Intern Med*. 2012;156(2):105-114.
22. Urashima M, Segawa T, Okazaki M, Kurihara M, Wada Y, Ida H. Randomized trial of vitamin D supplementation to prevent seasonal influenza A in schoolchildren. *Am J Clin Nutr*. 2010;91(5):1255-1260.
23. Sanders KM, Stuart AL, Williamson EJ, et al. Annual high-dose oral vitamin D and falls and fractures in older women: a randomized controlled trial. *JAMA*. 2010;303(18):1815-1822.
24. Trivedi DP, Doll R, Khaw KT. Effect of 4 monthly oral vitamin D<sub>3</sub> (cholecalciferol) supplementation on fractures and mortality in men and women living in the community: randomised double blind controlled trial. *BMJ*. 2003;326(7387):469.
25. Martineau AR. Bolus-dose vitamin D and prevention of childhood pneumonia. *Lancet*. 2012;379(9824):1373-1375.
26. Wilbur AK, Kubatko LS, Hurtado AM, Hill KR, Stone AC. Vitamin D receptor gene polymorphisms and susceptibility *M tuberculosis* in native Paraguayans. *Tuberculosis (Edinb)*. 2007;87(4):329-337.
27. Martineau AR, Timms PM, Bothamley GH, et al. High-dose vitamin D(3) during intensive-phase antimicrobial treatment of pulmonary tuberculosis: a double-blind randomised controlled trial. *Lancet*. 2011;377(9761):242-250.
28. Committee to Review Dietary Reference Intakes for Vitamin D and Calcium. *Dietary Reference Intakes for Calcium and Vitamin D*. Washington, DC: National Academies Press; 2011.